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Concise report

Seronegative polyarthritis revealing antisynthetase syndrome: a multicentre study of 40 patients

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Abstract

Objective. The aim of this study was to determine the frequency and characteristics of antisynthetase syndrome (ASS) revealed by polyarthritis.

Methods. First we conducted a retrospective single-centre study to assess the frequency of ASS patients who presented with polyarthritis without pulmonary and/or muscle symptoms. Secondly, we conducted a larger, multicentre study in order to describe the clinical characteristics of these patients. Exclusion criteria were the presence of RF, the presence of ACPA and overlap with another CTD.

Results. In the single-centre study, polyarthritis was the first manifestation in 12 of 45 ASS patients (27%). An additional 28 patients were collected for the multicentre study, resulting in a total population of 40 ASS patients who presented with polyarthritis. The mean delay from polyarthritis onset to ASS diagnosis was 27 months (S.D. 40). Pulmonary and muscle symptoms were uncommon at ASS diagnosis (40% and 32.5%, respectively) and were dramatically delayed [mean delay after polyarthritis onset of 41 months (S.D. 53) and 21 months (S.D. 14), respectively]. Mechanic's hands and cutaneous signs of DM occurred in 25% and 22.5%, respectively, with a mean delay of 10 months (S.D. 10) and 31 months (S.D. 21), respectively. When present (32%), RP was the earliest non-articular manifestation [mean delay 3 months (S.D. 23) after polyarthritis onset]. On HEp-2 cells, antinuclear and/or cytoplasmic fluorescence was found in 70% of cases, with specificity for various anti-aminoacyl tRNA synthetase (anti-ARS) antibodies.

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CLINICAL SCIENCE

Conclusion. ASS may be revealed by polyarthritis. To decrease the delay in diagnosis of ASS, pulmonary and muscle symptoms and anti-ARS antibodies might usefully be searched for in seronegative polyarthritis patients, especially in those with RP.

Key words: antisynthetase syndrome, rheumatoid arthritis, myositis, interstitial lung disease, Raynaud's phenomenon.

Introduction

Antisynthetase syndrome (ASS) is a heterogeneous entity that can include interstitial lung disease (ILD), inflammatory myopathy, joint involvement, RP, mechanic's hands (MH) and various cutaneous signs of DM associated with anti-aminoacyl tRNA synthetase (anti-ARS) antibodies. ILD, myositis and joint involvement are the most frequent clinical manifestations, with frequencies ranging from 70% to 90%, 65% to 92% and 60% to 95% of patients, respectively [1–7]. ILD and myositis can be isolated or precede other ASS manifestations [2, 3, 5, 8, 9]. For these reasons, screening for anti-ARS antibodies is recommended and routinely performed in seemingly isolated ILD and myositis [10, 11].

In contrast, testing for anti-ARS antibodies is not usually performed in isolated polyarthritis, even if tests for ACPA and RF are negative (defined as seronegative polyarthritis) and even if tests for ANA are negative and/or do not point to another systemic autoimmune disease. However, only two previous studies have reported that polyarthritis was the first and seemingly isolated ASS manifestation, in 21% and 32% of ASS patients, respectively, although neither study focused specifically on these patients [2, 3]. Mumm *et al*. [12] also described three ASS patients presenting with seronegative rheumatoid-like polyarthritis who did not have any pulmonary or muscle symptoms.

To confirm that joint involvement can be the first ASS manifestation, we retrospectively analysed all the ASS patients followed at our tertiary care centre and identified those who had presented with polyarthritis. Patients who had some confounding factors, such as an overlap syndrome with RA or another CTD that could account for the articular manifestations, were excluded from the study. As no previous studies have specifically described ASS patients presenting with polyarthritis, we then conducted a multicentre study among members of the French Club Rhumatismes et Inflammation in order to better assess the clinical characteristics of these patients.

Patients and methods

A single-centre retrospective study was first conducted at Lille University Hospital by analysing the demographic, clinical and laboratory data of all patients in the database of the Laboratory of Immunology who, between 2001 and 2013, had tested positive for anti-ARS antibodies (including anti-JO1, -PL7, -PL12, -EJ and -OJ; Immuno-Dot, Euroimmun, Lübeck, Germany). All patients were anonymously reported. The study was conducted in accordance with the recommendations of the Declaration of Helsinki and complied with the requirements of the French Commission Nationale de l'Informatique et des Libertés (DC-2008-642).

Patients were included if they had had at least two consecutive positive anti-ARS tests and an associated condition consistent with ASS, including pulmonary, muscle and/or joint involvement, as previously reported [6, 13]. All patients had undergone a high-resolution CT (HRCT) scan of the chest at ASS diagnosis: pulmonary involvement was defined as the presence of ILD on HRCT scan, with or without symptoms (cough, dyspnoea). Lung function evaluation was performed in all patients whose CT scan showed ILD. All patients had at least a creatine kinase (CK) level evaluation at ASS diagnosis and an electromyography (EMG) examination and/or a muscle biopsy in the case of muscular symptoms or increased CK level. Muscle involvement was defined as either myopathic changes on EMG, increased CK level or histological arguments for myositis on muscular biopsies, with or without symptoms (myalgia, muscle weakness). The diagnosis of polyarthritis was considered if a patient had inflammatory arthralgia (night pain and morning stiffness >30 min) and at least one synovitis (painful and swollen joints).

Patients were excluded if they had (i) a positive test for RF and/or ACPA or (ii) an overlap with another CTD according to the appropriate classification criteria for SLE, SS, SSc or mixed CTD [14–17].

Patients were considered to have had inaugural polyarthritis if they first had joint involvement without any pulmonary or muscle symptoms at the same time (±3 months), independently of the presence of other manifestations such as RP, MH and cutaneous signs of DM (periungual telangiectasia, periorbital erythema, Gottron's papules, heliotrope rash) that could have been retrospectively diagnosed and/or reported by patients.

In a second step, a multicentre study was conducted among members of the French Club Rhumatismes et Inflammation using a standardized form with the same inclusion and exclusion criteria as the single-centre study.

The results of chi-squared or Fisher's exact test (qualitative data) and Wilcoxon's test (continuous data) were considered significant for P-values < 0.05.

Results

Study population

Among the 45 patients who had manifestations related to ASS and no exclusion criteria in the single-centre study,

12 patients (27%) presented with isolated seronegative polyarthritis. Twenty-eight similar patients collected in the multicentre study were added to form group 1 ($n = 40$) (Fig. 1). The remaining 33 patients reported in the single-centre study (who had at least pulmonary and/or muscle inaugural symptoms) constituted group 2 and were compared with group 1. ASS diagnosis was maintained at the end of the follow-up for all patients [mean follow-up duration after ASS diagnosis 48 months (S.D. 44) in group 1, 75 months (S.D. 57) in group 2] and none of them developed any overlap syndrome with another CTD or tested positive for RF or ACPA during the follow-up.

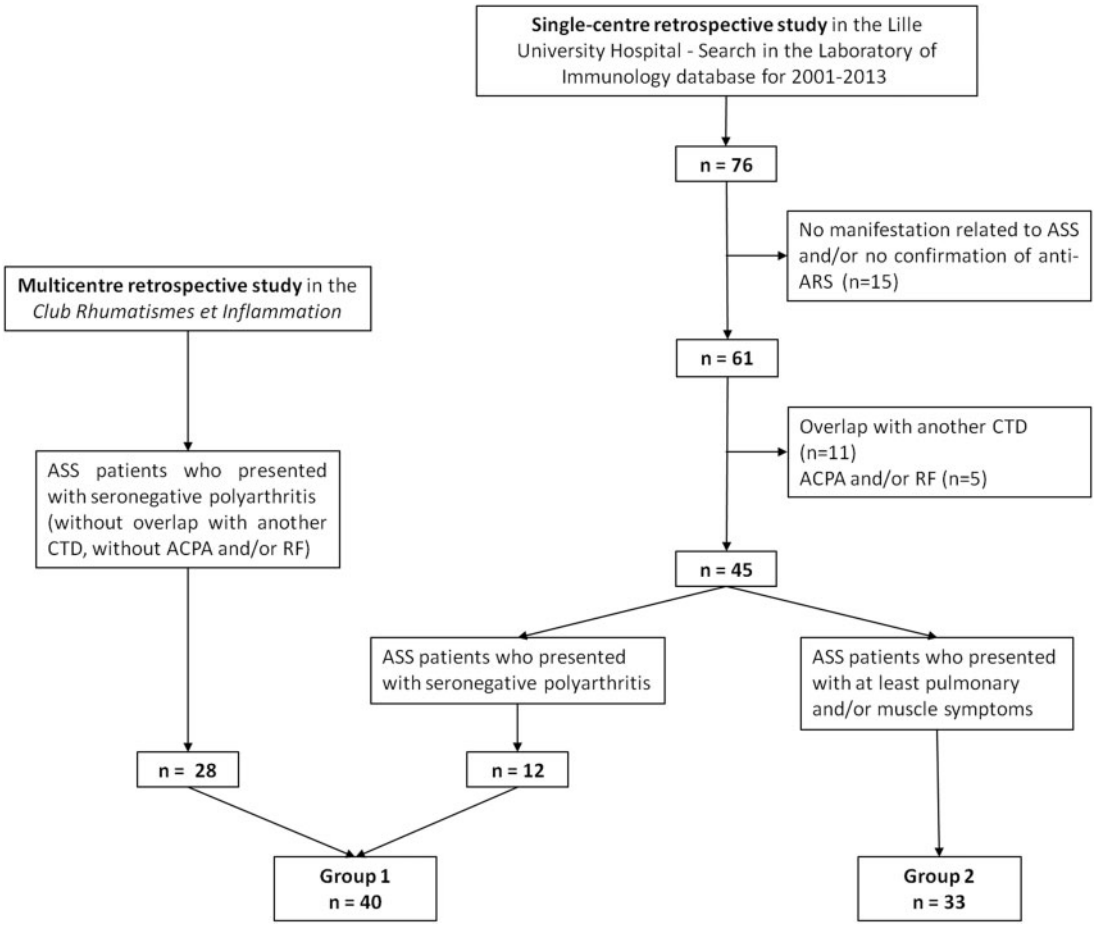
Joint involvement characteristics in ASS patients who presented with polyarthritis

All patients presented with distal symmetrical polyarthralgia with at least one synovitis or distal polyarthritis involving IP and/or MCP joints and/or wrists. Knees, elbows, shoulders, ankles, feet and hips were involved in 43%, 35%, 27%, 22%, 19% and 11% of patients, respectively (data available for 37 patients). Two of 35 patients (6%) had erosions on standard radiographs. Before ASS diagnosis, 24 patients (60%) had received at least one DMARD for seronegative polyarthritis: corticosteroids [$n = 21$ (52.5%)], MTX [$n = 7$ (18%)], HCQ [$n = 5$ (13%)], LEF [$n = 4$ (10%)], SSZ [$n = 2$ (5%)] and adalimumab [($n = 1$ (2.5%)]. The remaining 16 ASS patients had received conventional analgesics and/or NSAIDs.

Comparison of baseline characteristics at ASS diagnosis between patients who presented with polyarthritis (group 1) and patients with inaugural ILD and/or myositis (group 2)

There was a trend for a higher proportion of women in group 1 than in group 2 (82.5% *vs* 61%, $P = 0.06$). As defined, none of the patients in group 1 had inaugural pulmonary or muscular symptoms (see supplementary Table S1, available at *Rheumatology* Online). At ASS diagnosis, pulmonary symptoms were significantly less frequent in group 1 than in group 2 (40% *vs* 73%, $P = 0.009$) despite a similar ILD frequency on HRCT scan. In ASS patients whose CT scan showed ILD,

Fig. 1 Study flow chart



ASS: antisynthetase syndrome.

mean total lung capacity [81% (S.D. 22) of the predicted value in group 1, 78% (S.D. 27) in group 2] and forced vital capacity [80% (S.D. 26) in group 1, 78% (S.D. 28) in group 2] were similar, but patients in group 2 had a lower lung diffusing capacity for carbon monoxide (DLCO) [50% (S.D. 20)] than patients in group 1 [66% (S.D. 15), $P < 0.002$]. Likewise, muscle symptoms were significantly less frequent at ASS diagnosis in group 1 (32.5% *vs* 64%, $P = 0.01$) despite a similar frequency of muscle involvement. Overall, 19 patients (47.5%) in group 1 did not have any lung or muscle symptoms at ASS diagnosis (see supplementary Table S1, available at *Rheumatology* Online). The frequency of RP, MH and cutaneous signs of DM was similar in both groups (Table 1). Positive IIF on HEp-2 cells (nuclear and/or cytoplasmic) and speckled IIF were more frequent in group 1 than in group 2 (70% *vs* 36%, $P = 0.005$, and 45% *vs* 18%, $P = 0.02$, respectively). There was no difference in terms of the frequency of distribution of anti-ARS antibodies (Table 1).

Time of occurrence of non-articular clinical manifestations in ASS patients who presented with polyarthritis

In group 1, all patients had a follow-up duration of >6 months after polyarthritis onset and the mean follow-up duration was 75 months (S.D. 52). When present, MH, muscle symptoms, cutaneous signs of DM and pulmonary symptoms appeared a mean of 10 (S.D. 10), 21 (S.D. 14), 31 (S.D. 21) and 41 (S.D. 53) months after polyarthritis onset, respectively (see supplementary Table S2, available at *Rheumatology* Online). RP was present in 13 patients (32.5%) in group 1 at ASS diagnosis and 7 of them had RP or a recent history of RP before polyarthritis onset. Overall, when present, RP was the earliest non-articular ASS symptom, with a mean onset delay of 3 months (S.D. 23) after joint involvement. Finally, the mean delay from polyarthritis onset to ASS diagnosis was 27 months (S.D. 40) in ASS patients who presented with polyarthritis (group 1), which was significantly longer than in group 2 [18 months (S.D. 28) after the first ASS symptoms, $P = 0.04$].

Discussion

Our study shows that 27% of ASS patients presented with isolated polyarthritis as the first ASS manifestation. This result is in line with the case series available in the literature [2, 3, 12]. Furthermore, our large study of 40 ASS patients who presented with polyarthritis enables us to provide the first detailed description of such patients after having excluded confounding factors (such as a second CTD and/or positive RF and ACPA).

Interestingly, patients who presented with polyarthritis (group 1) had an unexpected lower frequency of pulmonary and muscle symptoms at ASS diagnosis when compared with previous reports [1–7] and the patients in group 2. Indeed, half of them (47.5%) had no pulmonary or muscle symptom. This difference is surprising because there was a similar ILD and muscle involvement frequency at ASS diagnosis in the patients of each of these groups.

Table 1 Characteristics of patients at ASS diagnosis (positive anti-ARS) in the two groups

	Group 1	Group 2	*P*-value
Demographics			
Individuals, *n*	40	33	
Females, *n* (%)	33 (82.5)	20 (61)	0.06
Age at ASS diagnosis, median (range), years	47.5 (20–83)	54 (22–74)	0.1
Delay from first ASS symptom to ASS diagnosis, mean (S.D.), months	27 (40)	18 (28)	0.04
Manifestations at ASS diagnosis, *n* (%)			
Pulmonary involvement	29 (72.5)	29 (88)	0.15
Pulmonary symptoms related to ILD	16 (40)	24 (73)	0.009
Cough	9 (22.5)	11 (33)	0.2
Dyspnoea	15 (37.5)	25 (76)	0.01
Severe dyspnoea (NYHA class III–IV)	5 (12.5)	13 (39)	0.02
Muscular involvement	22 (55)	23 (70)	0.5
Muscular symptoms related to myositis	13 (32.5)	21 (64)	0.01
Myalgia	13 (32.5)	19 (58)	0.048
Muscle weakness	9 (22.5)	17 (51)	0.02
Articular involvement	40 (100)	16 (48)	n.a.
RP	13 (32)	8 (24)	0.6
Mechanic's hands	10 (25)	10 (30)	0.8
Cutaneous signs of DM	9 (22.5)	5 (15)	0.5
Antisynthetase antibodies, *n* (%)			
JO1	30 (75)	20 (61)	0.3
PL7	3 (7.5)	6 (18)	0.3
PL12	5 (12.5)	5 (15)	0.7
EJ	2 (5)	2 (6)	1
Other antibodies, *n* (%)			
⩾1:80 IIF on HEp-2 cells (nuclear/cytoplasmic)[a]	28 (70)	12 (36)	0.005
Speckled fluorescence	18 (45)	6 (18)	0.02
Cytoplasmic fluorescence	5 (12.5)	3 (9)	0.7
Speckled + cytoplasmic fluorescence	2 (5)	0	0.5
Other fluorescence	2 (5)	3 (9)	0.6
Not available	1 (2.5)	0	1
Anti-Ro/SSA-52 kDa (TRIM21)	13 (32.5)	16 (48)	0.2
Anti-Ro/SSA-52 + 60 kDa	3 (7.5)	0	0.2
Anti-La/SSB	1 (2.5)	0	1

[a]IIF on human epidermoid cancer HEp-2 cells (Euroimmun, Lübeck, Germany) was considered positive if staining was found for a dilution ⩾1:80 whatever the pattern considered (nuclear or cytoplasmic). Group 1: patients with isolated seronegative polyarthritis as the first symptom. Group 2: patients who presented initially with at least pulmonary and/or muscle symptoms. anti-ARS: anti-ARS: anti-aminoacyl-tRNA-synthetase; ASS: antisynthetase syndrome; ILD: interstitial lung disease; n.a.: not applicable; NYHA: New York Heart Association.

A lower mean DLCO associated with more severe dyspnoea in patients whose CT scan showed ILD suggests more severe lung involvement in group 2 patients than in group 1 patients. ASS pulmonary and muscle symptoms (when present) were also dramatically delayed in group 1 when compared with group 2. These differences could be explained either by less aggressive disease or by the

efficacy of the treatments given to patients from the diagnosis of seronegative polyarthritis and prior to ASS diagnosis. As a result, ASS diagnosis was significantly delayed in patients who presented with polyarthritis [27 months (S.D. 40)] compared with patients who had inaugural pulmonary and/or muscle symptoms [18 months (S.D. 28), $P = 0.04$].

RP was present in 32% of patients with ASS revealed by polyarthritis. RP prevalence has recently been estimated to be lower (10%) in RA patients [18]. Our study suggests that RP could be considered as a red flag for clinicians managing patients with seronegative and apparently isolated polyarthritis.

In our study, positive ANA and speckled fluorescence were found more commonly in ASS patients who presented with polyarthritis than in other ASS patients. Likely due to the retrospective nature of our study, cytoplasmic fluorescence, which is evocative of the presence of ARS, was found in only a few patients in each group. Anti-Ro/SSA-52 kDa antibodies were found in 32.5% of ASS patients presenting with isolated polyarthritis (group 1), which was lower than the proportion (48%) in group 2. Although not statistically significant, these data are consistent with previous reports in which anti-Ro/SSA-52 kDa antibodies were associated with more severe pulmonary and muscle involvement in ASS patients [19].

Some potential selection biases may have been avoided despite the retrospective nature of the study. Patients included in the single-centre study were collected without selection according to their clinical manifestations, and there was no difference in terms of characteristics between patients from the Lille University Hospital and the other patients in group 1 (data not shown). It is crucially important to look for pulmonary and muscle involvement in an ASS patient: some less severe symptoms, such as cutaneous signs of DM, could have been underestimated, but all patients were managed in tertiary referral centres by clinicians specializing in ASS, which limits this risk. Among the 73 ASS patients included in the study, the frequencies of pulmonary and muscle involvement (79% and 62% of cases, respectively), polyarthritis (77%) and RP, MH and cutaneous signs of DM (29%, 27% and 19%, respectively) at ASS diagnosis were similar to those of previous case series reported in other centres [1–4, 7].

In conclusion, a significant proportion (27%) of our ASS patients had polyarthritis as the first manifestation. When compared with the classical ASS phenotype, including revealing ILD and/or myositis, these patients had a lower frequency of pulmonary and muscle symptoms at ASS diagnosis, which was significantly delayed. RP was the earliest non-articular symptom in ASS patients revealed by polyarthritis. As longer delay to diagnosis of ASS has been reported to be associated with a poor outcome [2], and as this could expose patients to TNF-α antagonists, which are not recommended in myositis [20] and can worsen ILD in ASS patients [21], a thorough search for pulmonary and muscle manifestations and testing for cytoplasmic IIF on HEp-2 cells and anti-ARS might usefully be considered in patients with seronegative polyarthritis, and especially in those with RP.

Rheumatology key messages

- A quarter of antisynthetase syndrome cases were revealed by isolated polyarthritis without pulmonary or muscle symptoms.
- Pulmonary and muscle symptoms may be rarer when polyarthritis is the first antisynthetase syndrome manifestation.
- Other antisynthetase syndrome manifestations and anti-aminoacyl tRNA synthetase should be carefully searched for in seronegative polyarthritis patients with RP.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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